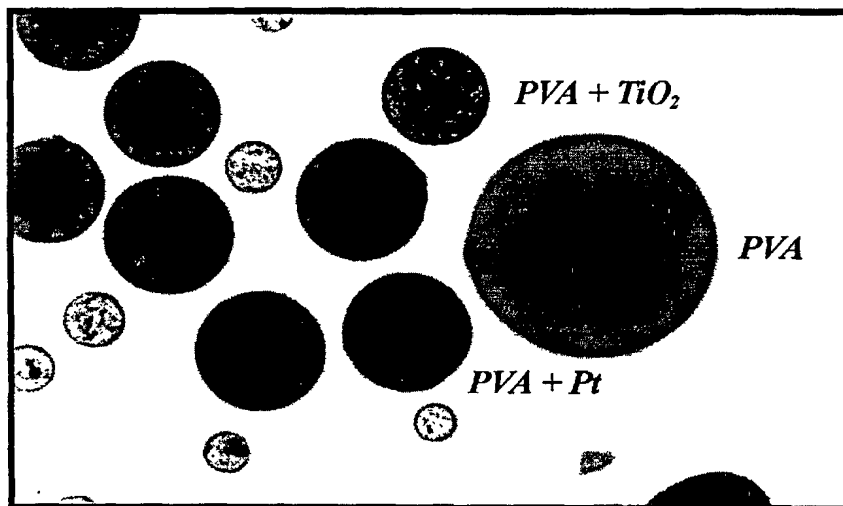




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 51/12, 49/00, 32/24, 47/30</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/66183</b> <b>(43) International Publication Date:</b> 9 November 2000 (09.11.00)
<b>(21) International Application Number:</b> PCT/KR00/00420 <b>(22) International Filing Date:</b> 3 May 2000 (03.05.00)  <b>(30) Priority Data:</b> 1999/15941                      3 May 1999 (03.05.99)                      KR  <b>(71) Applicant (for all designated States except US):</b> BOKWANG CO., LTD. [KR/KR]; Glass Tower Building, 30F, 946-1 Daichi-dong, Kangnam-ku, Seoul 135-280 (KR).  <b>(71)(72) Applicant and Inventor:</b> LEE, Kyu-Ho [KR/KR]; 7-201 Hyundai Villa, 172 Sangil-dong, Kandong-ku, Seoul 134-090 (KR).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> KIM, Kyung-Chae [KR/KR]; 130 Kongdan-dong, Kumi-shi, Kyungsangbuk-do 730-030 (KR).  <b>(74) Agent:</b> LEE, Kuiy, Dong; Seoul Building, 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR).		<b>(81) Designated States:</b> JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** VASCULAR EMBOLIC MATERIALS HAVING MULTIFUNCTIONS



*Bead form*

**(57) Abstract**

The present invention relates to a vascular embolic material for use in the treatment of an angiotropy of various tumors and a vascular malformation. Specifically, the present invention relates to a vascular embolic material having the specific morphological, physicochemical and radiological characteristics and multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material. The specific physicochemical and radiological characteristics of the vascular embolic material according to the present invention facilitate its clinical use and aid in the diagnosis before and after the embolization. Further, a local radiation treatment and anticancer treatment is possible and thus the therapeutic effect on said disorders can be enhanced.

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## VASCULAR EMBOLIC MATERIALS HAVING MULTIFUNCTIONS

### BACKGROUND OF THE INVENTION

5

#### 1. Field of the Invention

The present invention relates to a vascular embolic material for use in the treatment of an angiotropy of various tumors and a vascular malformation. Specifically, the present invention relates to a vascular embolic material having the specific morphological, physicochemical and radiological characteristics and multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

#### 15 2. Description of the Prior Art

Various vascular embolic materials are generally used to block an angiotropy or vascular malformation by infusing them via a fine vascular catheter while subjecting to angiography.

20

Various kinds of materials that are harmless to the human body and that which do not bring about adverse reactions are selected and used as a vascular embolic material depending on the purposes. However, it is now required in clinical therapeutics for the materials to have the deliverability of a specific drug, a radioactive isotope, etc., to a local region as the capability to block blood vessels.

25

### SUMMARY OF THE INVENTION

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It is, therefore, an object of the present invention to provide a new vascular embolic material having multifunction in the form of a bead or a sponge, which is harmless to the human body, hydrophilic and substantially permanent and moreover has the specific morphological, physicochemical and radiological characteristics and the deliverability of a specific drug and a radioactive isotope.

### BRIEF DESCRIPTION OF THE DRAWINGS

5        Figures 1a and 1b are drawings showing polyvinyl alcohol materials in the form of a bead and a sponge, respectively.

      Figures 2a and 2b are drawings showing the new vascular embolic materials in the form of a bead or a sponge, respectively.

10       Figure 3 is a drawing showing the result from a vascular embolization of a kidney of a rabbit.

      Figure 4 is an X-ray photographic image of a mixture of polyvinyl alcohol and  $\text{TiO}_2$ .

15       Figure 5 is a CT photographic image of a mixture of polyvinyl alcohol and  $\text{TiO}_2$ .

      Figure 6 is an MRI photographic image of a mixture of polyvinyl alcohol and  $\text{TiO}_2$ .

### DETAILED DESCRIPTION OF THE INVENTION

25       The object of the present invention is established by a vascular embolic material having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

      Therefore, the present invention is directed to a vascular embolic material  
30       having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

      According to the present invention, polyvinyl alcohol is primarily used as the polymer material constituting the vascular embolic material. Polyvinyl alcohol

- 3 -

having a molecular weight of 50,000 to 300,000 is preferably used. The metal material is preferred from the group consisting of  $\text{TiO}_2$ , Pt or a mixture of  $\text{TiO}_2$  and Pt. The mixing ratio of the polymer material and the metal material should preferably be 4-10:1.

5

The characteristics of the vascular embolic material according to the present invention will be described in greater detail in the following section.

## 10 **Morphological characteristics**

The vascular embolic material according to the present invention has either a bead or a sponge form, as shown in Figures 2a and 2b. Such vascular embolic material may be prepared in various sizes of 10 to 1000  $\mu\text{m}$  and easily infused into a very fine vascular catheter.

15

The result from a vascular embolization of a kidney of a rabbit (a pre-animal test) is shown in Figure 3.

20

## **Physicochemical characteristics**

The vascular embolic material according to the present invention is prepared using polyvinyl alcohol, with a molecular weight of 50,000 to 300,000, as a polymer material and  $\text{TiO}_2$  (99.95% of purity), Pt (99.9999% of purity) or a mixture of  $\text{TiO}_2$  and Pt having a size of 0.02 to 2  $\mu\text{m}$ . Such vascular embolic material has a specific gravity of 1.2 to 2.5, has a strong hydrophilicity and is harmless to the human body.

25

## 30 **Radiological characteristics**

Most vascular embolic materials currently used cannot be clearly recognized after the embolization since they appear transparent to radiation (X-ray).

- 4 -

However, the vascular embolic material according to the present invention includes a metal material that is visible to X-ray and thus the position can be seen. Therefore, the vascular embolic material according to the present invention shows an opaque image in an X-ray photography (see Figure 4).

Also, the vascular embolic material according to the present invention shows a high-density image in a computerized tomography (see Figure 5). Further, such vascular embolic material does not affect an image during a magnetic resonance imaging and shows a low resonance image (see Figure 6).

### **Multifunctionality**

An irradiation and an anticancer agent are generally used to treat a tumor. In order to enhance the therapeutic effect and reduce the possibility of an adverse reaction to the whole body, an irradiation of a radiation or infusion of an anticancer agent on a local legion is carried out in clinical therapeutics.

The vascular embolic material according to the present invention has an embolization effect of blocking an angiotropy. Further, such vascular embolic material may itself become isotoped by isotoping a metal material and thus having the deliverability of  $\beta$ -ray and  $\gamma$ -ray useful for the treatment. In addition, it is possible to add a drug such as an anticancer agent to the vascular embolic material to enhance the therapeutic effect on a local legion.

The vascular embolic material according to the present invention may be prepared by a method for drying in oil or a freeze drying method.

### **PREFERRED EMBODIMENT OF THE INVENTION**

The present invention will be described in greater detail by way of the following examples, which are not intended to limit the invention.

**Example 1**

5     Preparation of the vascular embolic material in the form of a bead by a method for drying in oil

7 % by weight of polyvinyl alcohol and 0.5 to 1.75 % by weight of Pt or TiO<sub>2</sub> powder were placed on a tertiary distilled water in a beaker while stirring at 700 rpm for 30 minutes. The solution was gradually heated from 30 °C to 80 °C while  
10     stirring for 2 to 3 hours and increasing the stirring speed to 1000 rpm in order to completely dissolve polyvinyl alcohol. Then, the solution was sealed and left for 12 hours or so at room temperature to remove the bubbles therein.

0.3 % by weight of sorbitan monostearate as a surfactant was added to 1 kg  
15     dispersion of liquid paraffin and gradually heated from room temperature to 70 °C and stirred at 1200 rpm. The mixed solution of polyvinyl alcohol and a metal material (Pt or TiO<sub>2</sub>) was infused into the stirred liquid by a syringe to make it a fine drop state. The dispersion was heated in a bath at 95 °C to 110 °C for 4 hours to gradually dry the drop and to prepare a mixture of polyvinyl alcohol and a metal in  
20     the form of a bead. The mixture was filtered out while maintaining the temperature of 60 ± 5 °C, repeatedly washing with n-hexane and drying under the reduced pressure. The dried materials were classified by size through a sieve.

Polyvinyl alcohol and a metal material were mixed so as that the ratio of the  
25     solid components is 4:1. When two kinds of metal materials were used together, the ratio between the two was varied depending on the purposes but the total amount between polyvinyl alcohol and a metal material was kept the same. Even the vascular embolic material in the form of a bead was prepared with polyvinyl alcohol only, the amount of polyvinyl alcohol was 8 % by weight and an anticancer agent was  
30     further added at an adequate amount.

**Example 2**

Preparation of the vascular embolic material in the form of a sponge by a freeze drying method

A mixed solution of polyvinyl alcohol and a metal material was prepared by the same method, as described in example 1. An equivalent amount of ammonium bicarbonate  $[(\text{NH}_4)_2\text{CO}_3]$  was added to the solution at room temperature so as that the ratio of the solid components is 1:1, and was mixed well. The bubbles formed at room temperature in vacuum state ( $10^3$  torr). The vessel was frozen by quenching with liquid nitrogen to  $-170^\circ\text{C}$  and this state was maintained for 10 minutes. It was confirmed that the materials in the vessel were completely frozen. Liquid nitrogen was removed and then moisture was further removed in vacuum state for 30 minutes. Thereafter, additionally moisture was removed by dipping into a mixed solution of an ice water and salt in vacuum state at  $-10^\circ\text{C}$  for 1 hour. After drying at room temperature in vacuum state for 4 hours, the resultant was dried again in a water bath at  $50^\circ\text{C}$  for 1 hour to completely remove moisture. Finally, liquid nitrogen was placed in the vessel and the materials in the vessel were pulverized and classified by size through a sieve.

Even when only polyvinyl alcohol was used without adding a metal material, the component ratio to ammonium bicarbonate was maintained in 1:1. An anticancer agent was further added in an adequate amount.

**Example 3**

Isotoping of the vascular embolic material according to the present invention

A metal material included in the vascular embolic material according to the present invention was irradiated in the core of a nuclear reaction (Hanaro) and a region where neutrons were generated in  $1.7 \times 10^{13} / \text{cm}^2 / \text{sec}$  for 1 minute and 10 minutes.  $\beta$ -ray and  $\gamma$ -ray emitted from the material was determined by a neutron activation analysis using Multi-Channel Detector and thus isotoping was confirmed.

The results are shown in Table 1.



- 7 -

Table 1

Polyvinyl alcohol + TiO<sub>2</sub> + Pt(2), after (n, gamma) reaction, NAA

5

Elements	Concentration	Radioneuclides	$\beta$ -ray	$\gamma$ -ray
Ti	11.60%	Ti-51	1.56 MeV (8%)	0.32 MeV (93%)
			2.17 MeV (92%)	0.61 MeV (1.2%)
				0.93 MeV (4.9%)
Pt	3.13	Pt-199	in-progress	
Na	0.56	Na-24	in-progress	
Cl	563 ppm	Cl-38	in-progress	
Al	130	Al-28	in-progress	
V	1.5	V-52	in-progress	

**Example 4**10 Anticancer effect of the vascular embolic material according to the present invention

5 to 50 mg of cisplatin among anticancer agents was added to the vascular embolic material according to the present invention and applied to a cultured cancerous cell. Then the anticancer effect was determined.

15

The results using 23.98 mg of cisplatin (NAA) are set forth in Table 2.

Table 2

Elements	Radioisotope	T <sub>1/2</sub>	Concentration
Pt	Pt-195m	96.48 hr	6.22±0.06 %
Au	Au-198	64.80	6.42±0.02 ppm
Na	Na-24	15.0	2.67±0.15 %
Cl	Cl-38	37.7 min	3.69±0.02 %

- 5           According to the present invention, a vascular embolic material for use in the treatment of a tumor and a vascular malformation is provided. The specific physicochemical and radiological characteristics of the material according to the present invention facilitate its clinical use and aid in the diagnosis before and after the embolization. Further, a local radiation treatment and anticancer treatment is
- 10 possible and thus the therapeutic effect on said disorders can be enhanced.

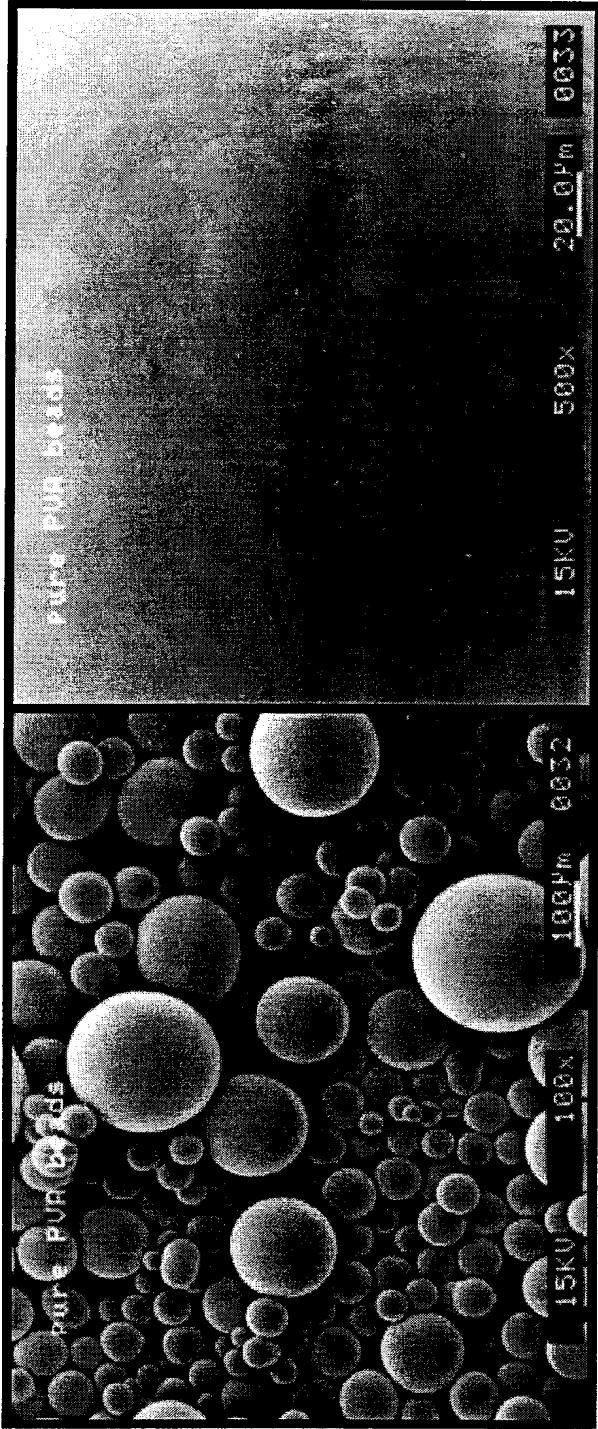
- 9 -

**What Is Claimed Is:**

1. A vascular embolic material having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.
- 5 2. The vascular embolic material according to Claim 1, wherein the hydrophilic polymer material is polyvinyl alcohol having a molecular weight of 50,000 to 300,000.
3. The vascular embolic material according to Claim 1, wherein the metal material is  
10 selected from the group consisting of  $\text{TiO}_2$ , Pt or a mixture of  $\text{TiO}_2$  and Pt.
4. The vascular embolic material according to Claim 1, wherein the mixing ratio of the hydrophilic polymer material and the metal material is 4-10:1.
- 15 5. The vascular embolic material according to Claim 1, which is isotoped by a neutron radiation.
6. The vascular embolic material according to Claim 1 further comprising a drug.
- 20 7. The vascular embolic material according to Claim 6, wherein the drug is an anticancer agent.

Fig. 1a

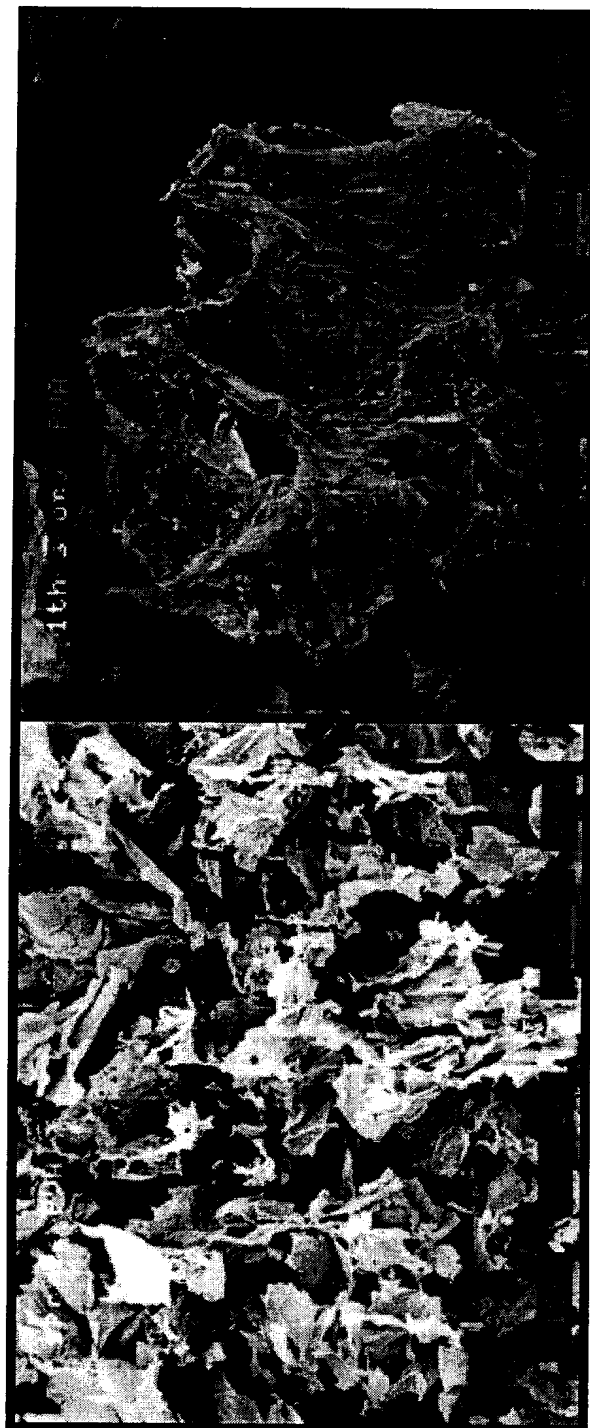
SEM



surface

2/7

Fig. 1b



SEM

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Fig. 2a

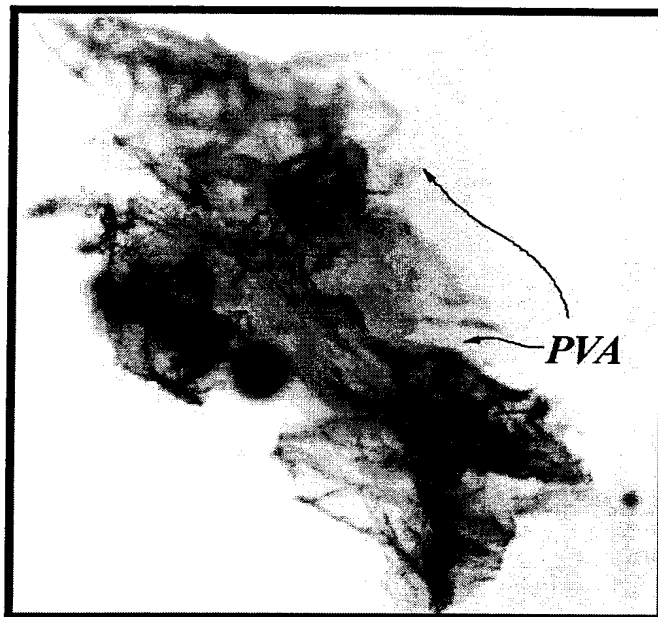
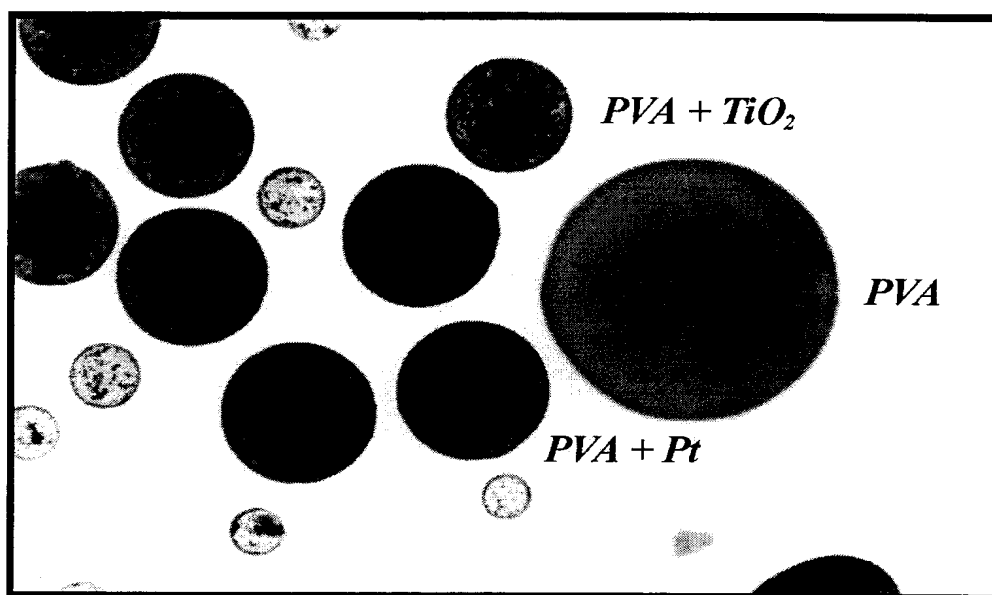
*Sponge form*

Fig. 2b

*Bead form*

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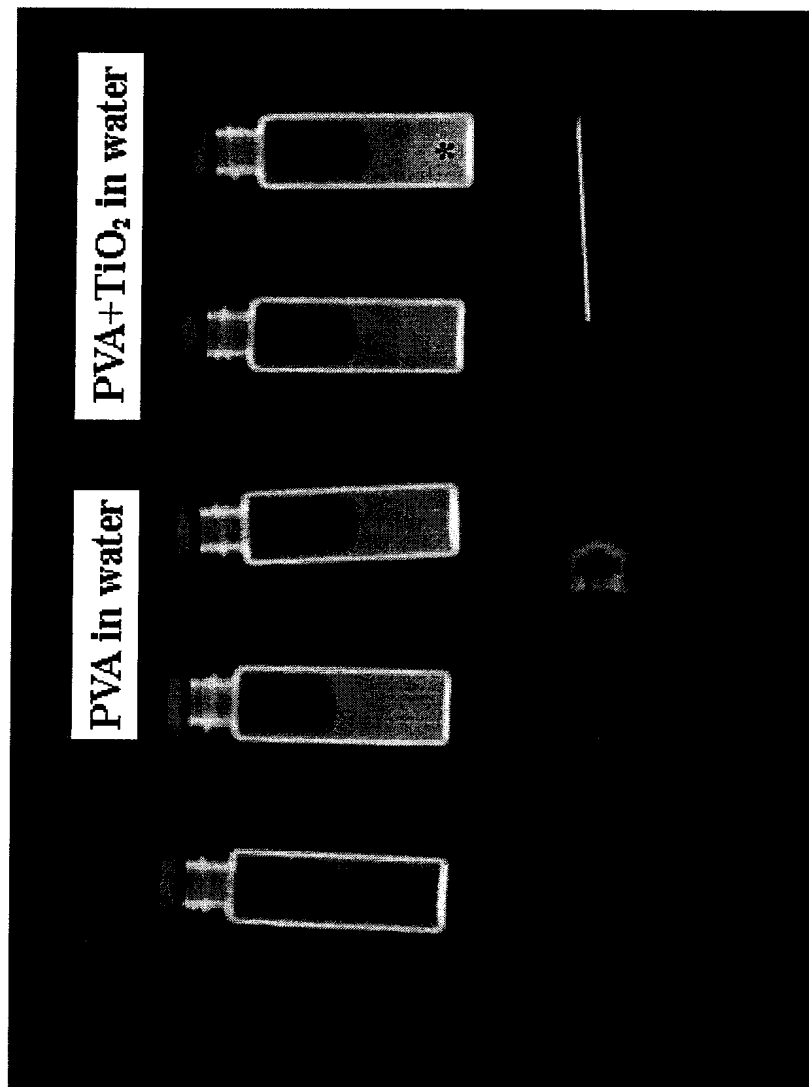
**Fig. 3**



PVA, 100 X LM

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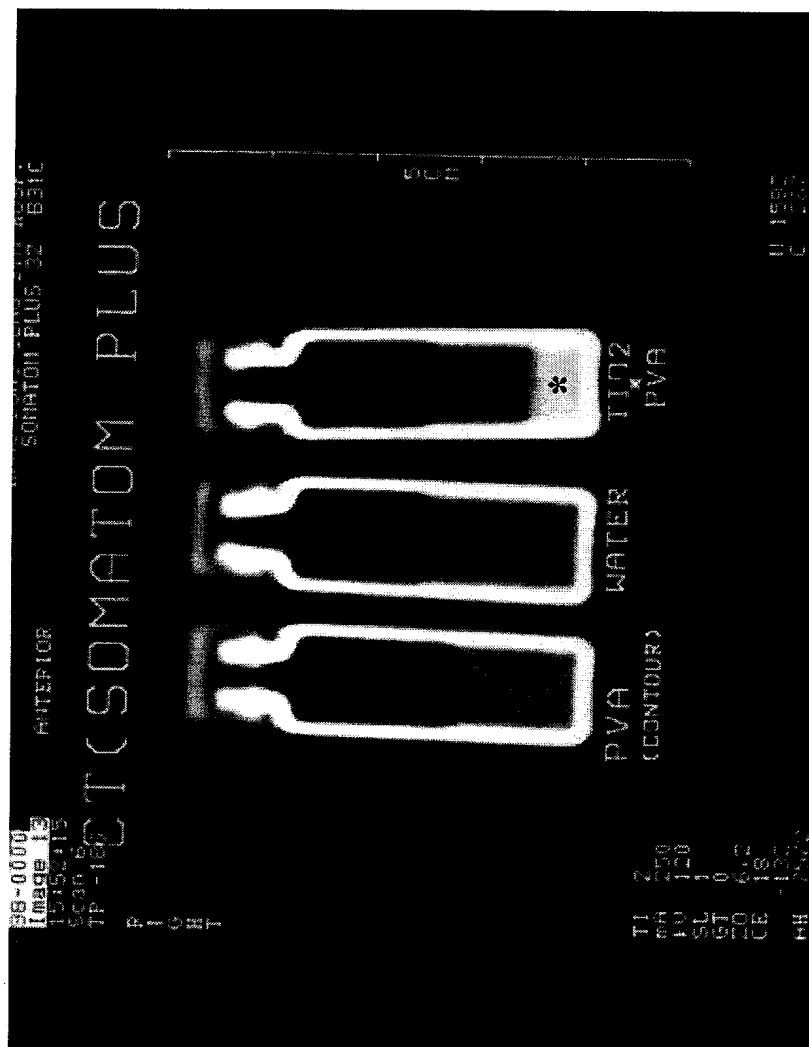
**Fig. 4**



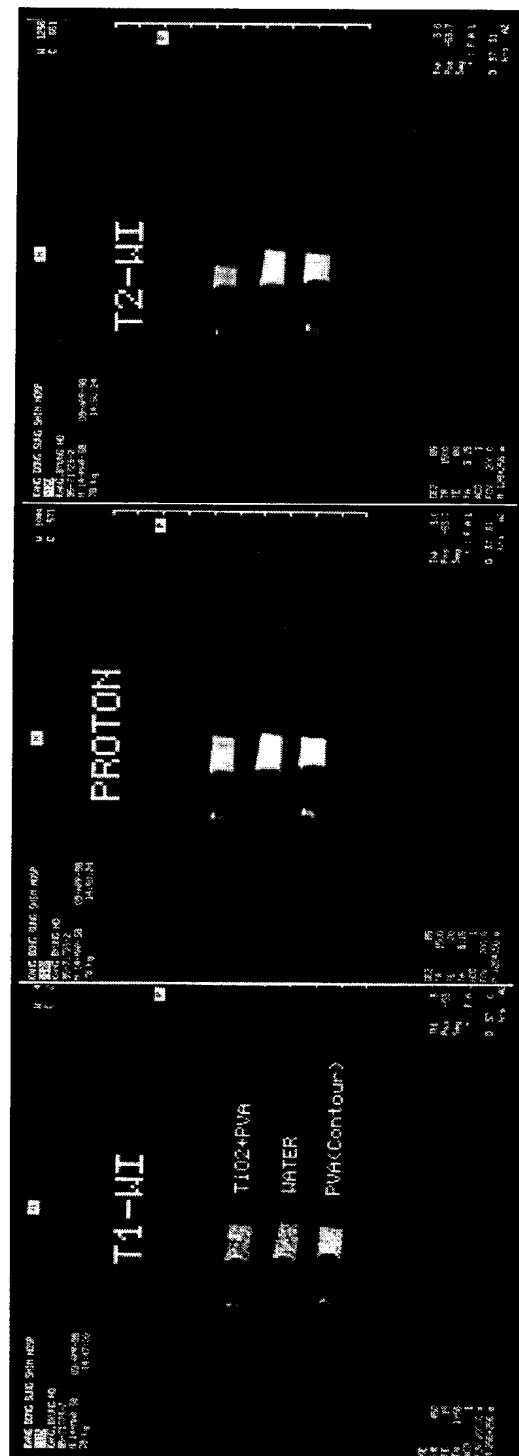


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Fig. 5



**Fig. 6**



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 00/00420

## CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: A 61 K 51/12, 49/00, 32/24, 47/30

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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>7</sup>: A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/12577 A1 (NYCOMED IMAGING AS) 18 March 1999 (18.03.99) abstract; page 5, line 14 - page 11, line 2; page 16, lines 1-8; claims.	1,2,5-7
X	JP 5000969 A (TAKEDA CHEM IND LTD) 8 January 1993 (08.01.93) (abstract) PAJ (online). London, U.K.: Derwent Pub. Ltd. Retrieved from EPOQUE, ABV-017251, ABD-1993	1,6,7
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☐ Further documents are listed in the continuation of Box C.

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Information on patent family members

International application No.

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				WO	A1	9922775	14-05-1999

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(74) Agent: **LEE, Kuiy, Dong**; Seoul Building, 114-31, Uni-  
dong, Chongro-ku, Seoul 110-350 (KR).

(81) Designated States (national): JP, US.

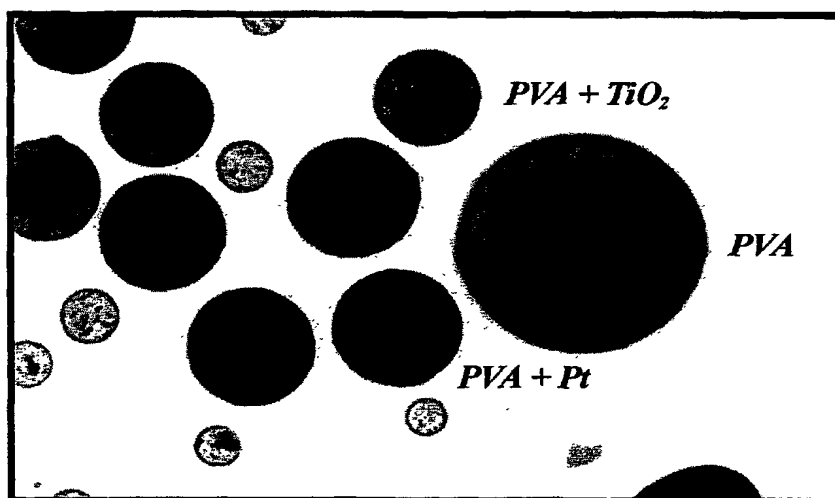
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[Continued on next page]

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**(15) Information about Correction:**

see PCT Gazette No. 04/2001 of 25 January 2001, Section II

INTERNATIONAL SEARCH REPORT

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Information on patent family members

International application No.

PCT/KR 00/00420

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